Stereoselective Synthesis of Yohimbine Alkaloids from Secologanin

By RICHARD T BROWN and SIMON B PRATT
(*Chemistry Department, The University, Manchester* M13 9PL)

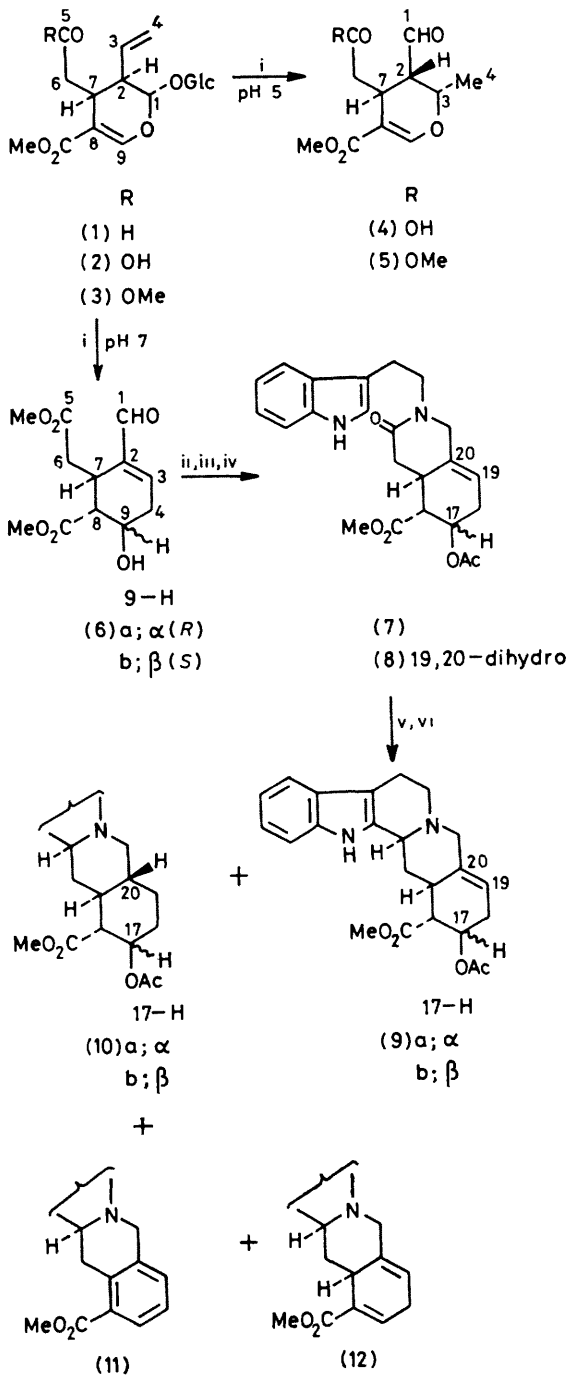
Summary Glucolysis of methyl secoxyloganin (**3**) at pH 7 has afforded, *via* a biogenetically patterned vinylogous aldol reaction, two key substituted cyclohexenes (**6**) from which the acetates of β-yohimbine (**10a**), yohimbine (**10b**), and their 19,20-dehydro derivatives (**9**) have been synthesised in addition to dihydrogambirtannine (**11**)

IN a previous paper[1] we reported that, from the glucolysis in pH 5 aqueous buffer of secoxyloganin (**2**) [made by oxidation of secologanin (**1**)] elenolic acid (**4**) was obtained and subsequently converted into heteroyohimbine alkaloids As expected, the corresponding methyl ester (**3**) behaved similarly to give (**5**), but we have now found that simply by carrying out the reaction at pH 7, the aglucone can be induced to undergo selectively an alternative rearrangement leading to a carbocyclic product (**6**) Not only does this type of cyclisation represent the closest analogy yet for the *in vivo* formation of ring E in yohimbine alkaloids, but these can also readily be synthesised from (**6**)

Thus, on treatment of (**3**) with β-glucosidase in pH 7·0 buffer the only material isolated (*ca* 60% yield) was a new product, isomeric with (**5**) but more polar and showing significant spectral and chemical differences Its u v maximum was at 228 nm rather than at the 237 nm typical of the β-alkoxyacrylate system in (**5**) and this, together with i r bands at 1690 and 1645 cm^{-1}, suggested an αβ-unsaturated aldehyde chromophore The i r spectrum still had a carbonyl absorption at 1730 cm^{-1} but a distinctive

TABLE 300 MHz N m r spectra in $(CD_3)_2CO$

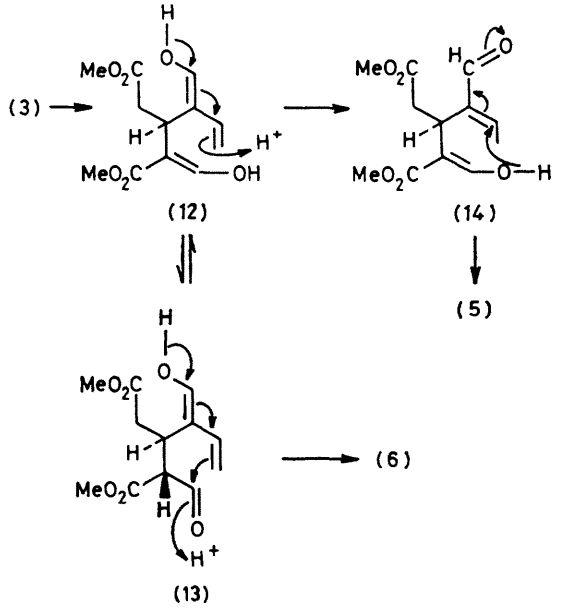
	Major epimer	(**6a**)	Minor epimer	(**6b**)
H	τ	*J*/Hz (coupled proton)	τ	*J*/Hz (coupled proton)
1	0 45	s	0 44	s
3	2·98	5(4a), 3 5(4b), 1(7)	2 98	4(4a), 4(4b), 1(7)
4a	7·24	19 5(4b), 5 5(9), 5(3), 2(7)	7 18	19 5(4b), 5(9), 4(3), 2(7)
4b	7·50	19·5(4a), 7(9), 3 5(3), 2·5(7)	7 39	19 5(4a), 7(9), 4(3), 1·5(7)
6a	7·00	16 5(6b), 8(7)	*ca* 7 0	?
6b	7·34	16·5(6a), 3·5(7)	*ca* 7 3	?
7	6 65	8(6a), 7·5(8), 3·5(6b), 2 5(4b), 2(4a), 1(3)	6 55	5 5(7), 2(4a), 1 5(4b), 1(3), ?(6a, b)
8	7·06	8(9), 7·5(7)	6 94	5 5(7), 3·5(9)
9	5·74	8(8), 7(4b), 5·5(4a)	5·56	7(4b), 5(4a), 3 5(8)
O*Me* × 2	6·25, 6·31	s	6·25, 6·31	s



Reagents: i, β-glucosidase; ii, Ac_2O–pyridine; iii, tryptamine; iv, $NaCNBH_3$; v, $POCl_3$, heat; vi, $NaBH_4$.

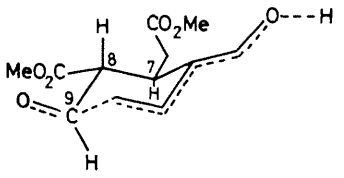
new feature was a strong absorption at 3500 cm^{-1} indicating a hydroxy group, which was confirmed by formation of a monoacetate. Eventually the 300 MHz n.m.r. spectrum revealed that the material was actually a mixture of two C-9 epimers in a ratio of *ca.* 3 : 1, a complete analysis (see Table) enabling us to assign structure and stereochemistry (**6a**) to the major and (**6b**) to the minor product. In particular the *trans–trans* triaxial relationship of the hydrogens on C-7, -8, and -9 in the major isomer was evident from their relatively large mutual couplings. The minor component could only be the 9β(*S*)-epimer (**6b**) since the 7-H,8-H coupling was again compatible with an approximate *trans*-diaxial orientation, whereas 9-H showed only a small *cis a–e* coupling with 8-H. In both cases useful analogies were afforded by similar protons in shikimic acid.[2]

Corroboration of the structural and stereochemical assignments was obtained by conversion of (**6**) into known yohimbine alkaloids based on the procedure used in Woodward's reserpine synthesis.[3] Acetylation, condensation with tryptamine, and reduction with sodium cyanoborohydride yielded a mixture (*ca.* 1 : 1) of unsaturated and saturated lactams (**7**) and (**8**). Subsequent Bischler–Napieralski cyclisation with $POCl_3$ and reduction with sodium borohydride gave two major and four minor products which were separated by t.l.c. The major alkaloids were identified as β-yohimbine acetate (**10a**) and its previously unknown 19,20-dehydro analogue (**9a**), and two of the minor compounds as yohimbine acetate (**10b**) and 19,20-dehydroyohimbine acetate (**9b**). The ratio of β-yohimbine to yohimbine derivatives was *ca.* 3 : 1, reflecting the relative proportion of (**6a**) to (**6b**). Other minor products were dihydrogambirtannine (**11**) and a trace of material with M^+ 334 assumed to be its precursor (**12**) formed by elimination of acetic acid from (**9**). Interestingly, reduction of the 19,20-double bond affords essentially only 20β-stereochemistry, just as in the catalytic hydrogenation of (**9b**) to (**10b**).[4] Hence, further reduction of the mixture at the lactam stage would be expected to increase the effective yield of (**10**).



SCHEME

Presumably, the carbocyclic ring in (**6**) is formed by a vinylogous aldol reaction of a tautomer (**13**) of the ring-opened aglucone (Scheme) which at pH 7 competes effectively with the rearrangement of another tautomer (**12**) to the conjugated aldehyde (**14**) and thence to (**5**), the latter



FIGURE

process being preferred at pH 5 The obvious pH dependence is finely balanced, and at pH 6 both types of product are formed in comparable amounts A striking feature in the production of (**6**) is the high degree of chiral induction only *R* stereochemistry at C-8 and largely *R* at C-9 This stereoselectivity can be attributed to a chair-like transition state for the cyclisation (Figure) in which the large C-7 and C-8 substituents are exclusively equatorial, as is preferentially the incipient hydroxy group at C-9

We have already established that strictosidine, the natural precursor for monoterpenoid indole alkaloids, can be stereoselectively converted *in vitro* into heteroyohimbine alkaloids by a biomimetic process rather analogous to the above formation of (**5**) from (**3**) [5] Since the cyclisation to (**6**) constitutes a good model for the biosynthesis of yohimbine alkaloids, work is in progress to obtain these from strictosidine in a comparable fashion

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